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Relationship between proximal sodium reabsorption and excretion of calcium, magnesium and phosphate

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Relationship between proximal sodium reabsorption and excretion of calcium, magnesium and phosphate. The relationship between sodium reabsorption by the proximal tubule, measured by micropuncture techniques, and the urinary excretion of calcium, magnesium, and phosphate was determined following a number of experimental maneuvers known to increase sodium excretion. Following intravenous infusion of saline or Ringer's solution and the renal arterial infusions of acetylcholine and prostaglandin E_1, proximal sodium reabsorption was significantly decreased while the fractional clearances of Na, Ca, Mg and PO_4 were significantly increased. Following the intravenous infusion of hyperoncotic albumin and the renal arterial infusion of parathyroid hormone, proximal sodium reabsorption was significantly decreased and the fractional clearances of Na and PO_4 were significantly increased. The fractional clearances of Ca and Mg were not increased following these infusions. Following the renal arterial infusion of bradykinin and prostaglandin E_2, there was no significant change in proximal sodium reabsorption or in the fractional clearance of PO_4 while the fractional clearances of Na, Ca and Mg were significantly increased. It was concluded that changes in the fractional clearance of PO_4 are related to decreases in sodium reabsorption by the proximal tubule. Changes in the fractional clearances of Ca and Mg were not consistently associated with changes in proximal sodium reabsorption, suggesting that the excretion of these ions is primarily controlled by nephron segments distal to the proximal tubule.

Relation entre la réabsorption proximale du sodium et l'excrétion de Ca, Mg et PO_4. La relation entre la réabsorption du sodium par le tube proximal, mesurée par microponction, et l'excrétion urinaire de Ca, Mg et PO_4 at été déterminée à la suite de plusieurs manoeuvres expérimentales connues pour augmenter l'excrétion du sodium. L'injection intraveineuse de soluté salé physiologique ou de solution de Ringer et les injections intra-artérielles rénales d'acétylcholine et de prostaglandine E_1 diminuent significativement la réabsorption proximale du sodium en même temps que les clearances fractionnelles de Na, Ca, Mg et PO_4 sont significativement augmentées. L'injection intra-artérielle rénale d'hormone parathyroïdienne et l'injection intra-veineuse d'albumine hyperoncotique diminuent significativement la réabsorption proximale du sodium en même temps que les clearances fractionnelles de Na et PO_4 sont significativement augmentées. Les clearances fractionnelles de Ca et Mg ne sont pas augmentées par ces injections. L'injection intra-artérielle rénale de bradykinine et de prostaglandine E_2 ne détermine pas de modification significative de la réabsorption proximale du sodium et de la clearance fractionnelle de PO_4 alors que les clearances fractionnelles de Na, Ca et Mg augmentent significativement. Il est conclu que les modifications de la clearance fractionnelle de PO_4 sont en rapport avec les diminutions de la réabsorption de sodium par le tube proximal. Les modifications des clearances fractionnelles de Ca et Mg ne sont pas uniformément associées à des variations de la réabsorption proximale du sodium, ce qui suggère que l'excrétion de ces ions est contrôlée principalement par des segments de néphron situés en aval du tube proximal.

Under a variety of conditions Walser [1] found that when sodium excretion increased there was a proportional increase in calcium excretion. Other investigators have also found a similar relationship between sodium excretion and the excretion of magnesium and phosphate. Suki et al [2], Massry et al [3, 4] and Antoniou et al [5] have hypothesized that the increased excretion of these ions following volume expansion is related to an inhibition of proximal sodium reabsorption. This hypothesis is based on the observation that volume expansion inhibits sodium reabsorption by the proximal tubule [6] and that the majority of calcium and magnesium [7, 8], and probably all phosphate [9], reabsorption occurs in the proximal tubule. Further support for an association between phosphate excretion and sodium reabsorption by the proximal tubule has been presented by Agus et al [10]. Based on measurements of sodium and phosphate reabsorption by the proximal tubule and urinary phosphate excretion following saline or parathyroid hormone infusion, these authors have recently hypothesized that changes in phosphate excretion are primarily related to changes in sodium reabsorption by the proximal tubule.

Based on studies with diuretics, Eknoyan, Suki and Martinez-Maldonado [11] concluded that those diuretics which affect the loop of Henle and distal nephron segments caused greater increases in calcium

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and magnesium excretion than those diuretics which primarily affect the proximal tubule. In contrast, phosphaturia was associated with the diuretics having a proximal site of action.

Since the majority of the evidence in support of a relationship between proximal sodium reabsorption and the urinary excretion of calcium, magnesium and phosphate is indirect, the present study was designed to directly examine this relationship. Sodium reabsorption by the proximal tubule was determined by micropuncture techniques following a number of experimental maneuvers known to increase sodium excretion.

Methods

Mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 mg/kg) and prepared for clearance and micropuncture measurements as previously described for our laboratory [12]. In dogs which received a renal arterial infusion, a curved 23-gauge needle was placed into the left renal artery retrograde to the direction of blood flow. Patency of this needle was maintained by the continuous infusion of 0.9% sodium chloride solution at 1 ml/min. During experimental periods a solution containing the appropriate hormone in isotonic saline was substituted for this infusion. An infusion was given to establish and maintain a plasma inulin concentration of 1 mg/ml and a plasma para-aminohippurate (PAH) concentration of 0.02 mg/ml. The sustaining infusion was given at 1 ml/min in isotonic saline. Micropuncture measurements and clearance determination of glomerular filtration rate (GFR), renal plasma flow (RPF), and the urinary excretion of sodium, calcium, magnesium and phosphate were made during three 15-minute periods of continued hydropenia. After completion of the initial clearance and micropuncture measurements, one of the following experimental protocols was performed:

Control studies (9 dogs). After one hour had elapsed, the micropuncture and clearance measurements were repeated.

Saline loading (12 dogs). Saline was infused intravenously at 1 ml/min/kg for 20 minutes and continued thereafter at 0.5 ml/min/kg. Sixty minutes after the start of saline infusion, micropuncture and clearance measurements were repeated.

Ringer's loading (17 dogs). A Ringer's solution (containing Na, 138 mEq/liter; K, 3.7 mEq/liter; Ca, 6 mg/100 ml; Mg, 2.2 mg/100 ml; PO_4, 6 mg/100 ml; HCO_3, 25 mmoles/liter; Cl, 123 mEq/liter; glucose, 100 mg/100 ml; and bubbled with 95% O_2 and 5% CO_2) was infused intravenously following the same protocol as in the saline loading experiments.

Hyperoncotic albumin infusion (10 dogs). Salt-poor human serum albumin (25%) was infused intravenously (6.5 ml/kg) over 20 minutes. After an additional 40-minute equilibration period, the clearance and micropuncture determinations were repeated.

Parathyroid hormone infusion (12 dogs). Extract of bovine parathyroid glands (0.05 μ/kg/min) was infused into the renal artery of the micropunctured kidney. Sixty minutes after the start of the infusion, clearance and micropuncture measurements were repeated.

Acetylcholine infusion (10 dogs). Acetylcholine (2 μg/kg/min) was infused into the renal artery of the micropunctured kidney. Fifteen minutes after the start of the infusion, clearance and micropuncture measurements were repeated.

Bradykinin infusion (15 dogs). Bradykinin (0.75 μg/kg/min) was infused into the renal artery of the micropunctured kidney. Fifteen minutes after the start of the infusion, clearance and micropuncture measurements were repeated.

Prostaglandin E_1 infusion (11 dogs). Prostaglandin E_1 (0.15 μg/kg/min) was infused into the renal artery of the micropunctured kidney. Fifteen minutes after the start of the infusion, clearance and micropuncture measurements were repeated.

Prostaglandin E_2 infusion (9 dogs). Prostaglandin E_2 (0.15 μg/kg/min) was infused into the renal artery of the micropunctured kidney. Fifteen minutes after the start of the infusion, clearance and micropuncture measurements were repeated.

Late proximal tubule segments were identified by the use of lissamine green dye injections or by the injection of small nonocclusive oil droplets as previously described [13].

Tubule fluid samples were collected at a rate which was sufficient to collect all the volume flow at the puncture site and to hold a column of stained castor oil distal to the puncture to prevent retrograde flow [14]. The concentration of inulin in the tubule fluid was determined in duplicate by the microfluorometric method [15]. Fractional reabsorption (FR) of sodium and water by the proximal tubule was calculated from the following expression:

$$FR = 1 - \left(\frac{P}{TF}\right)_{In}$$

Blood samples were collected at the midpoint of the 15-minute urine collection periods. Inulin in plasma and urine was measured by the anthrone method. The PAH concentration in plasma and urine was measured by the method of Harvey and Brothers [16]. Renal plasma flow was calculated from the clearance and extraction of PAH. Sodium and potassium concen-

trations in plasma and urine were measured by flame photometry. Phosphate in plasma and urine was measured by the method of Young [17]. Calcium and magnesium in plasma and urine were measured by atomic absorption spectroscopy. Ultrafilterable calcium and magnesium were determined in four dogs which were saline-loaded and four dogs which received an infusion of hyperoncotic albumin. Ultrafilterable calcium and magnesium were obtained from anaerobic blood samples, centrifuged in an atmosphere of 5% CO_2 and 95% O_2 at 4°C. The plasma was then placed in a filter cone (Amicon) and centrifuged in an atmosphere of 5% CO_2 and 95% O_2. The ultrafiltrate was analyzed for calcium and magnesium by atomic absorption spectroscopy.

Electrolyte excretion was expressed as the electrolyte clearance per 100 ml of GFR and is referred to throughout this paper as the fractional clearance. In calculating the fractional clearance of calcium and magnesium, it should be noted that the plasma concentration of these ions was used. Where changes in ultrafilterable Ca and Mg might have been expected (saline and hyperoncotic albumin infusion), those variables were measured.

The data for each variable were averaged for the clearance periods during hydropenia and for the clearance periods during the experimental periods. Student's *t* test for paired comparisons was used for statistical analysis with a *P* value of less than 0.05 considered to represent a statistically significant change.

Results

The results of these studies are summarized in Tables 1 and 2 and in Fig. 1.

Control dogs. In the nine dogs which received no additional experimental intervention, there were no significant changes in any of the renal clearance indexes which were studied. Except for a small decrease in plasma Mg concentration (-0.09 ± 0.02 mg/100 ml), no change in the measured plasma electrolyte concentrations was detected. Fractional sodium reabsorption by 35 proximal tubules during the initial period (0.30 ± 0.02) was not significantly different from that obtained during the recollection period (0.30 ± 0.02).

Saline infusion. In the 12 dogs which received an isotonic saline infusion, there were no significant changes in renal plasma flow or glomerular filtration rate. Plasma sodium concentration and the percent of ultrafilterable calcium and magnesium were not changed while the changes in plasma calcium (-1.4 ± 0.1 mg/100 ml), magnesium (-0.31 ± 0.04 mg/100 ml), and phosphate (-1.13 ± 0.2 mg/100 ml)concentrations were significant. The fractional clearances of sodium ($+3.1 \pm 0.49$ ml/min/100 ml of GFR), cal-

Table 1. Summary of clearance data

Experimental Group	Glomerular filtration rate, *ml/min*		Renal plasma flow, *ml/min*		Fractional electrolyte clearance, *ml/min/100 ml GFR*							
					Na		Ca		Mg		PO_4	
	H[a]	E[b]	H	E	H	E	H	E	H	E	H	E
Control dogs	29	26	126	95	1.10	0.82	1.04	0.75	7.4	5.9	20.6	23.8
$N=9$	±6	±6	±17	±10	±0.29	±0.22	±0.26	±0.09	±1.9	±1.4	±3.1	±4.4
Saline loading	44	49	195	211	0.50	3.60	0.48	1.60	4.7	7.9	21.6	30.7
$N=12$	±6	±8	±26	±31	±0.11	±0.60	±0.07	±0.20	±0.6	±0.9	±3.9	±4.1
Ringer's loading	28	29	114	112	0.86	4.78	0.58	1.95	6.2	14.6	21.5	32.7
$N=17$	±2	±3	±8	±11	±0.26	±0.79	±0.13	±0.37	±0.9	±1.5	±3.2	±3.9
Hyperoncotic albumin	30	33	129	183	0.39	0.87	0.51	0.48	3.9	3.2	11.7	20.9
$N=10$	±4	±4	±16	±26	±0.07	±0.17	±0.09	±0.08	±0.7	±0.7	±2.1	±2.3
Parathyroid hormone	37	38	132	129	0.50	1.15	0.68	0.57	6.5	4.8	15.2	30.7
$N=12$	±3	±4	±17	±16	±0.08	±0.19	±0.18	±0.10	±1.2	±1.0	±2.1	±2.8
Acetylcholine	35	42	124	181	0.60	3.02	0.93	2.07	4.9	10.0	12.2	22.7
$N=14$	±4	±5	±9	±8	±0.16	±0.73	±0.29	±0.45	±1.0	±2.0	±3.7	±3.0
Bradykinin	25	25	97	118	0.86	1.84	0.71	1.36	7.6	11.1	21.7	23.3
$N=15$	±4	±3	±14	±18	±0.20	±0.26	±0.09	±0.16	±0.8	±1.9	±3.8	±2.9
Prostaglandin E_1	27	27	91	121	0.64	2.32	0.68	1.54	5.7	9.8	16.4	23.6
$N=11$	±2	±2	±8	±13	±0.13	±0.32	±0.23	±0.25	±0.9	±1.1	±2.3	±2.5
Prostaglandin E_2	27	26	83	102	1.22	2.15	0.49	0.95	6.8	8.1	22.5	23.4
$N=9$	±2	±2	±10	±14	±0.21	±0.39	±0.09	±0.22	±1.2	±1.6	±2.8	±2.7

[a] H = hydropenia.
[b] E = experimental.

Table 2. Summary of plasma electrolytes

Experimental Group	Sodium, *mEq/liter*		Phosphorus, *mg/100 ml*		Magnesium, *mg/100 ml*		Calcium, *mg/100 ml*		% Ultrafilterable Ca		% Ultrafilterable Mg	
	H[a]	E[b]	H	E	H	E	H	E	H	E	H	E
Control dogs	152 ±1	153 ±2	6.55 ±0.37	6.47 ±0.37	1.69 ±0.05	1.60 ±0.05	9.5 ±0.1	9.4 ±0.1	—	—	—	—
Saline loading	146 ±2	148 ±2	6.01 ±0.33	4.88 ±0.23	1.72 ±0.08	1.41 ±0.05	9.9 ±0.1	8.5 ±0.1	57 ±2	61 ±4	76 ±3	76 ±4
Ringer's loading	152 ±1	152 ±1	6.38 ±0.32	6.53 ±0.37	1.63 ±0.03	1.55 ±0.02	9.6 ±0.1	8.7 ±0.1	—	—	—	—
Hyperoncotic albumin	150 ±2	151 ±2	5.89 ±0.38	6.10 ±0.45	1.69 ±0.05	1.68 ±0.06	9.4 ±0.1	9.8 ±0.1	58 ±3	57 ±5	74 ±6	69 ±5
Parathyroid hormone	151 ±2	153 ±2	6.43 ±0.44	6.27 ±0.44	1.66 ±0.05	1.59 ±0.05	9.8 ±0.1	9.8 ±0.2	—	—	—	—
Acetylcholine	149 ±1	149 ±1	6.58 ±0.45	6.44 ±0.34	1.75 ±0.06	1.70 ±0.04	9.7 ±0.2	9.6 ±0.2	—	—	—	—
Bradykinin	148 ±1	148 ±1	6.60 ±0.33	6.70 ±0.36	1.69 ±0.03	1.62 ±0.03	9.7 ±0.1	9.5 ±0.2	—	—	—	—
Prostaglandin E_1	151 ±2	153 ±2	5.83 ±0.31	6.11 ±0.34	1.64 ±0.06	1.55 ±0.07	9.6 ±0.1	9.3 ±0.1	—	—	—	—
Prostaglandin E_2	150 ±1	151 ±1	5.62 ±0.53	5.84 ±0.49	1.57 ±0.07	1.46 ±0.07	9.5 ±0.1	9.3 ±0.1	—	—	—	—

[a] H = hydropenia.
[b] E = experimental.

cium (+1.12 ± 0.19 ml/min/100 ml of GFR), magnesium (+3.2 ± 0.7 ml/min/100 ml of GFR), and phosphate (+9.1 ± 3.4 ml/min/100 ml of GFR) were significantly increased. Fractional sodium reabsorption by the proximal tubule decreased significantly (−46 ± 6%) following saline infusion.

Ringer's infusion. In 17 dogs infusion of an isotonic Ringer's solution did not produce any significant changes in glomerular filtration rate or renal plasma flow. There were no significant changes in the plasma concentration of sodium or phosphate while the changes in plasma calcium (−0.85 ± 0.05 mg/100 ml) and magnesium (−0.08 ± 0.2 mg/100 ml) concentrations were significant. The changes in the fractional clearances of sodium (+3.91 ± 0.63 ml/min/100 ml of GFR), calcium (+1.37 ± 0.29 ml/min/100 ml of GFR), magnesium (+8.4 ± 0.9 ml/min/100 ml of GFR), and phosphate (+11.2 ± 3.4 ml/min/100 ml of GFR) were significant. Fractional sodium reabsorption by the proximal tubules was significantly decreased (−48 ± 5%) following Ringer's infusion.

Hyperoncotic albumin infusion. In ten dogs which received hyperoncotic albumin, renal plasma flow was significantly increased while glomerular filtration rate remained unchanged. Except for a significant (+0.5 ± 0.1 mg/100 ml) increase in plasma calcium concentration, there were no significant changes in any of the other plasma electrolyte values. There were significant increases in the fractional clearances of sodium (+0.48 ± 0.14 ml/min/100 ml of GFR) and phosphate (+9.2 ± 2.8 ml/min/100 ml of GFR) while the fractional clearances of calcium and magnesium were not significantly changed. Fractional sodium reabsorption by the proximal tubule decreased significantly (−28 ± 7%) following albumin infusion.

Parathyroid extract (PTE) infusion. The infusion of PTE into the renal artery (0.05 U/min/kg) of 12 dogs caused no significant change in glomerular filtration rate or renal plasma flow. Except for a significant decrease in plasma magnesium concentration (−0.7 ± 0.02 mg/100 ml), there were no significant changes in the measured plasma electrolyte values. The fractional clearances of sodium (+0.65 ± 0.16 ml/min/100 ml of GFR) and phosphate (+15.6 ± 1.9 ml/min/100 ml of GFR) were increased significantly while the fractional clearance of calcium was not significantly altered. The fractional clearance of magnesium was significantly decreased (−1.7 ± 0.5 ml/min/100 ml of GFR). Fractional sodium reabsorption by the proximal tubule was significantly decreased (−13 ± 4%) following PTE infusion.

Acetylcholine infusion. The renal arterial infusion of acetylcholine (2 μg/min/kg) in 14 dogs caused a significant increase in glomerular filtration rate (+6.2 ± 2.1 ml/min) and in renal plasma flow (+57 ± 4 ml/min). No significant change in mean arterial blood pressure was obtained. No significant changes occurred in any of the measured plasma electrolyte values. The

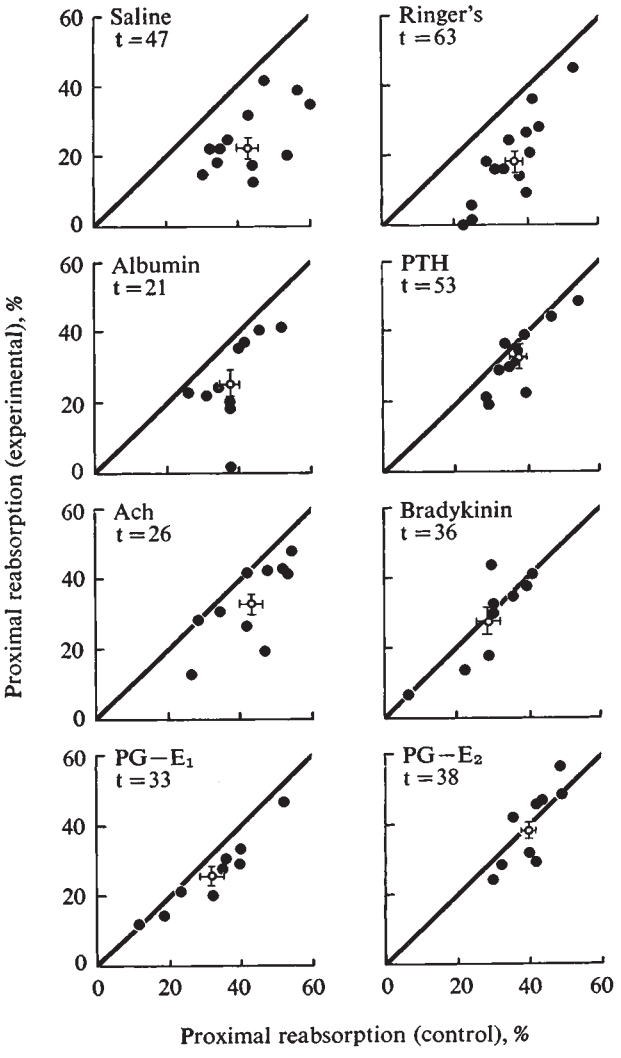

Fig. 1. *Summary of micropuncture results before and after the various experimental maneuvers (see text for explanation).* The *solid points* represent the mean value for each dog, the *open circle* represents the group mean ±1 SE, and *t* is the number of tubules from which both control and recollection samples were obtained. The *solid lines* represent the line of no change.

changes in the fractional clearances of sodium (+2.42 ± 0.69 ml/min/100 ml of GFR), calcium (+1.14 ± 0.46 ml/min/100 ml of GFR), magnesium (+5.07 ± 1.13 ml/min/100 ml of GFR) and phosphate (+10.6 ± 3.9 ml/min/100 ml of GFR) were significant. Fractional sodium reabsorption by the proximal tubule was significantly decreased (−24 ± 8%) by the infusion of acetylcholine.

Bradykinin infusion. The infusion of bradykinin (0.75 μg/kg/min) into the renal artery of 15 dogs caused a significant increase in renal plasma flow (+21 ± 7 ml/min) but there was no change in glomerular filtration rate or mean arterial pressure. Except for a small decrease in plasma magnesium concentration (−0.07 ± 0.03 mg/100 ml), there were no significant changes in the measured plasma electrolytes. The changes in the fractional clearances of sodium (+0.98 ± 0.22 ml/min/100 ml of GFR), calcium (+0.65 ± 14 ml/min/100 ml of GFR) and magnesium (+3.5 ± 1.4 ml/min/100 ml of GFR) were significant. No significant change in the fractional clearance of phosphate was observed. Fractional reabsorption by the proximal tubule was not significantly changed (−5 ± 4%) following bradykinin infusion.

Prostaglandin E_1 infusion. The infusion of prostaglandin E_1 (0.15 μg/min/kg into the renal artery of 11 dogs caused a significant increase in renal plasma flow (+30 ± 9 ml/min) but no change in glomerular filtration rate or mean arterial pressure. No significant change occurred in any of the plasma electrolyte values. The changes in the fractional clearances of sodium (+1.68 ± 0.29 ml/min/100 ml of GFR), calcium (+0.86 ± 0.15 ml/min/100 ml of GFR), magnesium (+4.03 ± 1.02 ml/min/100 ml of GFR) and phosphate (+7.2 ± 1.9 ml/min/100 ml of GFR) were significant. Fractional sodium reabsorption by the proximal tubule was significantly decreased (−17 ± 4%) following the infusion of prostaglandin E_1.

Prostaglandin E_2 infusion. The infusion of prostalandin E_2 (0.15 μg/min/kg) into the renal artery of eight dogs caused a significant increase in renal plasma flow (+19 ± 4 ml/min) but no change in glomerular filtration rate or mean arterial blood pressure. No significant changes occurred in any of the plasma electrolyte values. The changes in the fractional clearances of sodium (+0.93 ± 0.23 ml/min/100 of GFR) and calcium (+0.46 ± 0.14 ml/min/100 ml of GFR) were significant. The change in the fractional clearance of magnesium (+1.25 ± 0.62 ml/min/100 ml of GFR) following prostaglandin E_2 infusion was not significant. However, this increase was significant when compared to control animals. No significant change in the fractional clearance of phosphate was observed. Fractional reabsorption by the proximal tubule was not significantly changed (0 ± 4%) following the infusion of prostaglandin E_2.

The relationship of changes in phosphate, calcium and magnesium excretion to changes in sodium reabsorption by the proximal tubule is presented in Fig. 2. The fractional clearance of phosphate was the only excretory variable which was consistently associated with changes in fractional sodium reabsorption by the proximal tubule. However, no statistically significant correlation was obtained when the data were analyzed by linear, exponential or parabolic regression analysis. The fractional clearances of calcium and magnesium were dissociated from changes in fractional sodium reabsorption by the proximal

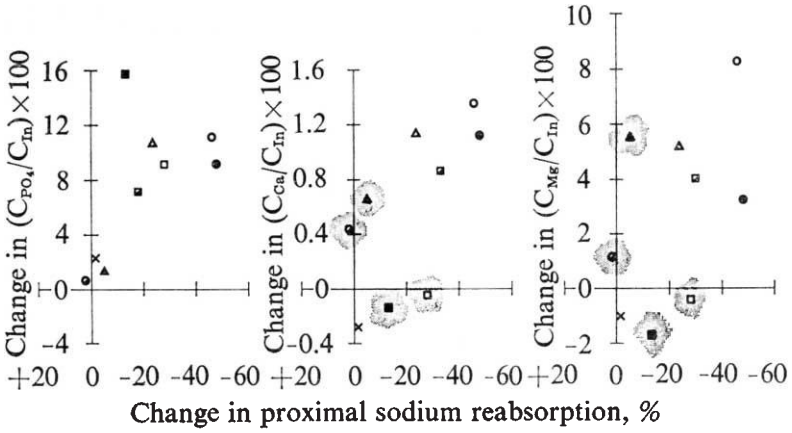

Fig. 2. *The relationship between mean changes in sodium reabsorption by the proximal tubule and mean changes in the fractional clearances of phosphate* (left), *calcium* (center) *and magnesium* (right) *following the various experimental maneuvers.* The *symbols surrounded by shadowing* represent experiments for which a significant change in the fractional clearance of Ca, Mg, or P was not associated with a significant change in proximal sodium reabsorption or vice versa. × = control ($N=9$); ● = Ringer's solution ($N=17$); ○ = saline solution ($N=12$); □ = albumin ($N=10$); ■ = parathyroid hormone ($N=12$); △ = acetylcholine ($N=14$); ▲ = bradykinin ($N=15$); ◪ = prostaglandin E_1 ($N=8$); ◑ = prostaglandin E_2 ($N=7$).

tubule following the infusion of hyperoncotic albumin, parathyroid hormone, bradykinin and prostaglandin E_2. Consequently, no significant correlation was obtained between changes in fractional calcium or magnesium excretion and changes in proximal sodium reabsorption.

Discussion

The findings in this study demonstrate that increases in urinary phosphate excretion are associated with decreases in sodium reabsorption by the proximal tubule. In agreement with previous studies, the infusion of isotonic saline or Ringer's solution, acetylcholine or parathyroid hormone decreased sodium reabsorption by the proximal tubule [6, 10, 18] and increased phosphate excretion [10, 19, 20]. Similarly, the infusion of hyperoncotic albumin and the renal arterial infusion of prostaglandin E_1 inhibited sodium reabsorption by the proximal tubule [21, 22] and increased phosphate excretion, thus lending further support to an association between proximal sodium reabsorption and urinary phosphate excretion.

Conversely, no detectable changes occurred in either sodium reabsorption by the proximal tubule[1] or urinary phosphate excretion following the renal arterial infusion of prostaglandin E_2 or bradykinin. That prostaglandin E_2 did not inhibit proximal sodium reabsorption is in agreement with the observation of Fülgraff and Meiforth [23], who were unable to demonstrate an effect of prostaglandin E_2 on proximal sodium reabsorption using either free-flow micropuncture techniques or the split-droplet method. The absence of a significant decrease in sodium reabsorption by the proximal tubule following bradykinin infusion is in agreement with previous observations by Stein et al [24] and Dirks and Seely [25]. Although no increase in phosphate excretion was observed following bradykinin infusion in the present study, Ahumada and Massry [19] have reported that bradykinin increased phosphate excretion. The reason for the discrepancy between the present findings and those of Ahumada and Massry is not apparent. However, their data indicated that, for similar increases in sodium excretion, phosphate excretion was increased more by acetylcholine than by bradykinin. Although the dose of bradykinin used in the present study was similar to that used by Ahumada and Massry, they reported increases in fractional sodium clearances two to five times higher than those observed in this study or in the study of Stein et al [24]. Considering the large increase in sodium excretion which they observed, there may have been some decrease in sodium reabsorption by the proximal tubule in their experiments which could have accounted for the small phosphaturia. These observations support the hypothesis that phosphate excretion is closely associated with sodium reabsorption by the proximal tubule rather than with sodium excretion.

Phosphate reabsorption has been considered to occur almost totally in the proximal tubule [9, 26–29] although Amiel, Kuntziger and Richet [26] concluded that there may also be significant distal reabsorption of phosphate. Microinjection studies of

[1] It must be recognized that changes in fractional sodium reabsorption by the proximal tubule of less than 8% are not detectable by present micropuncture methodology.

Staum, Hamburger and Goldberg [28] indicate that greater than 95% of ^{33}P-phosphate injected into late segments of the proximal tubule is recovered in the urine. These authors concluded that phosphate reabsorption does not occur in the distal convoluted tubule or collecting duct. The microperfusion studies of Murayama, Morel and LeGrimellec [29] indicate no transport of phosphate in the loop of Henle. Thus, changes in phosphate excretion probably represent changes in reabsorption of phosphate in the proximal tubule. Based on a close association between phosphate and sodium reabsorption by the proximal tubule, Agus et al [10] hypothesized that phosphate reabsorption by the proximal tubule may be secondary to sodium reabsorption by the proximal tubule and factors which enhance phosphate excretion would do so by primarily inhibiting sodium reabsorption by the proximal tubule. Therefore, a linear correlation between proximal sodium reabsorption and urinary phosphate excretion would be expected. Although the present findings support an association between phosphate reabsorption and sodium reabsorption by the proximal tubule, there was no statistically significant correlation between proximal sodium reabsorption and urinary phosphate excretion when the data were analyzed by linear, exponential or parabolic regression analysis. The reason for this lack of a significant correlation is that the increase in phosphate clearance was significantly greater following PTH infusion ($+15.5 \pm 1.3$ ml/min/100 ml of GFR) than that following saline infusion ($+9.1 \pm 3.4$ ml/min/100 ml of GFR), while the decrease in proximal sodium reabsorption was significantly less following PTH infusion ($-13 \pm 4\%$) than that following saline infusion ($-46 \pm 5\%$). These findings indicate that parathyriod hormone has a greater effect on phosphate excretion than on sodium reabsorption by the proximal tubule. Agus et al [10] also showed that the increase in the phosphate excretion following PTH infusion was twice that following saline infusion. Additional evidence which suggests that phosphate excretion is not determined entirely by sodium reabsorption by the proximal tubule was also obtained by comparing the effect of saline infusion and hyperoncotic albumin infusion. The phosphaturia following saline infusion was not significantly different from the phosphaturia following hyperoncotic albumin infusion. However, the decrease in sodium reabsorption by the proximal tubule following saline infusion was significantly greater than the decrease in sodium reabsorption by the proximal tubule following hyperoncotic albumin infusion.

Thus, the present findings do not support the hypothesis that phosphate reabsorption is secondary to sodium reabsorption by the proximal tubule. However, the present results do not indicate the precise mechanism(s) responsible for phosphate reabsorption. Indeed, several possible mechanisms have been proposed which could explain the results obtained in this study. There may be a significant amount of phosphate reabsorption occurring along the loop of Henle or distal nephron [26, 27]. Thus, alterations in distal phosphate reabsorption could alter any relationship between phosphate excretion and proximal sodium reabsorption. There is also evidence suggesting that there may be a phosphate reabsorptive system in the proximal tubule which is independent of proximal sodium reabsorption [28]. Finally, both of the mechanisms just mentioned may be operating under different physiological conditions.

Calcium and magnesium. The increase in calcium and magnesium excretion following the infusion of saline, Ringer's solution, acetylcholine or prostaglandin E_1 was associated with decreases in proximal sodium reabsorption. Such observations have led other investigators [2–5] to suggest that increases in calcium and magnesium excretion are a result of an inhibition of proximal sodium reabsorption. However, parathyroid hormone infusion, which inhibited proximal sodium reabsorption, did not increase the fractional excretion of calcium or magnesium. Since Murayama et al [29] have demonstrated a large bidirectional flux for calcium and sodium along the proximal tubule, a close association of sodium and calcium reabsorption by the proximal tubule would be expected. Agus et al [30] have recently demonstrated that parathyroid hormone causes a similar inhibition in both sodium and calcium reabsorption by the proximal tubule. Thus, the inhibition of proximal sodium reabsorption in their studies was associated with an increase in calcium delivery from the proximal tubule which did not appear in the urine. The inhibition of proximal sodium reabsorption by the infusion of hyperoncotic albumin possibly causes a similar inhibition of proximal reabsorption of calcium without concomitant increases in calcium excretion. Additional support for an important role in the nephron segments distal to the proximal tubule in determining calcium and magnesium excretion was the finding of an increase in calcium and magnesium excretion without an inhibition of sodium reabsorption by the proximal tubule following bradykinin or prostaglandin E_2 infusion. However, since no direct measurement of calcium or magnesium reabsorption by the proximal tubule was obtained, a specific inhibition of calcium and magnesium reabsorption by the proximal tubule independent of sodium reabsorption must also be considered. Nevertheless, there was no correlation between changes in the

excretion of calcium and magnesium and changes in proximal sodium reabsorption.

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